REMARKS/ARGUMENTS

Applicants note with appreciation that a number of rejections have been withdrawn in the present Office Action and that claims 27-31 are indicated as allowed. The remaining claims stand rejected for allegedly being anticipated and/or obvious over the prior art. The rejections are addressed below.

Rejection under 35 U.S.C. § 102(b)

Claims 1 and 9 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Smidt 2000 (Nature Neuroscience 3:337-341).

The Examiner states that Smidt teaches a nucleic acid fragment encoding an Lmx1b protein, and that the mouse Lmx1b is referred to as GenBank accession number AF078166 (Page 2 of the Office action). The Examiner takes the position based on alignments presented in the Office Action that the nucleic acids of the invention would hybridize to the Lmx1b gene described by Smidt. As explained below, Applicants experiments described in the specification demonstrate that, in fact, mRNAs from the two genes can be distinguished in hybridization assays. Moreover, Applicants respectfully submit that the evidence provided by the Examiner does not support the rejection.

Applicants note that Example 2 on page 39 of the specification provides an experiment of *in situ* hybridization in which the expression of gene of the present invention (Lmx1a), as well as the expression of the Lmx1b gene were examined using nucleic acids specific to mRNAs from each of these genes. The hybridization conditions used in the experiment were 0.2x SSC, 68°C (*see*, page 39, line 33), and the expression of the two genes was separately detected as shown in Figure 2. As noted on page 39, the sample was further washed in 1x TBST at room temperature (r.t.), but the "1x TBST" contains 150 mM NaCl that is nearly equivalent to "1x SSC" which contains 150 mM sodium chloride and 15 mM sodium citrate. Therefore, the stringency of the washing in 1x TBST at r.t. should be far lower than that in 0.2x SSC at 68°C, and therefore, the washing in 1x TBST at r.t. would not be a determinative factor of the hybridization stringency when the sample is previously washed in 0.2x SSC at 68°C. Thus, it

is clear that a nucleic acid specific to sequences recited in the claims will not hybridize to Lmx1b under these conditions.

To expedite the prosecution, claims 1, 9 and 12 have been amended to recite "68°C" instead of "65°C" based on the experiments described in Example 2, and recite that the probe nucleic acid hybridizes to SEQ ID NO: 13, 15, or 17 and does not hybridize to the nucleic acid of SEQ ID NO: 19 (see amended claims 1 and 9). The sequence of SEQ ID NO: 19 represents the mouse Lmx1b cDNA (see page 27, line 32 of the specification) and is identical to the sequence of AF078166 as shown by the attached alignment in Appendix A.

In addition, to further clarify the claims the term "polynucleotide" has been replaced with the term "nucleic acid." This amendment merely distinguishes between nucleic acid and the "polynucleotide" to which it is hybridized. No new matter is added by these amendments.

In view of the above explanation and the claim amendments, it is clear that the Lmx1b gene of Smidt does not hybridize to the recited sequence under the hybridization conditions set forth in the claims. The rejection over Smidt is therefore rendered moot and should be withdrawn..

Moreover, the alignments and other evidence provided by the Examiner do not support the rejection. On page 2 of the Office Action, the Examiner asserts that the claims "are considerably broader" because they are not limited to the recited sequences. Applicants respectfully disagree. The claims merely encompass a reasonable scope around the sequences described here. It is well known in the art that it is not necessary to use a full length of a nucleic acid as a probe for specific hybridization. For example, Smidt uses a 223b-fragment (bp 915-1137) of TH cDNA as a probe for detecting the TH expression, and a 285b-fragment (bp 1-285) of Ptx3 cDNA as a probe for detecting the Ptx3 expression (see page 340 of Smidt). Using the full length cDNA is not necessary for specific hybridization, and the person of ordinary skill in the art would use fragments of a cDNA as a probe without undue experiment because the specific hybridization using a fragment of a cDNA is routine and widely performed in a number of experiments in this art field as exemplified in Smidt.

Applicants note that the Examiner incorrectly states that the claims encompass used of "nucleic acids that hybridize to nucleic acids encoding SEQ ID NO:14, 16, or 18" (sentence bridging pages 2-3). However, this phrase has been deleted from the original claims in the previous amendment filed on January 6, 2010.

The Examiner further states that "[t]he alignments shown below indicates that AF078166, i.e. the nucleic acid encoded by Smidt's cDNA, will hybridize to any of SEQ ID NO:13, 15, or 17" (page 3, emphasis added). The Examiner also states that "the three alignments shown above indicate that the sequences will hybridize" (page 8). Applicants respectfully point out that the alignments shown by the Examiner do not support the rejection.

The Examiner provides three alignments. The first two alignments ("SEQ ID NO:13 aligned with AF078166" and "SEQ ID NO:15 aligned with AF078166") are "sense strand vs. sense strand" alignments. However, the third alignment (SEQ ID NO:17 aligned with AF078166) is the "sense strand vs. antisense strand" alignment with a number of gap-insertions, seemingly a typical alignment when two nonspecific sequences are forcibly aligned. The Examiner then argues that SEQ ID NO:17 will ***hybridize*** to AF078166 based on this alignment. Such an alignment does not provide evidence of the two sequences to hybridize, however. To properly show that the two molecules hybridize, the Examiner must show where the sense and antisense strands are ***complimentary,*** not identical. Such evidence is therefore inappropriate to support the rejection.

The Examiner also points to multiple long stretches of sequence identity in the first two alignments (i.e. SEQ ID NO:13 and 15) (page 8 of the Office Action). The Examiner also notes the existence of "the long stretches of identity across the entirety of the sequences" (page 3, lines 4-5). Applicants note, however, that the sequence similarity of SEQ ID NO:13 and 15 to AF078166 is not so high. Applicants enclose the alignments of SEQ ID NO:13 vs. AF078166, and SEQ ID NO:15 vs. AF078166 which show that the sequence similarities are 70% and 71%, respectively (see attached alignments in Appendix A).

It well know in the art that such low sequence identity is generally recognized as evidence that two sequences do ***not*** hybridize under stringent conditions. In support, Applicants

provide a publication explaining that "in general, if the percentage of matching nucleotides is lower than 70 percent, the two single-stranded nucleic acid molecules are considered nonhomologous and any hybridisation is considered nonstringent" (R.H.J. Schlegel, Dictionary of Plant Breeding, Second Edition, CRC Press, 2009, p. 191, copy enclosed, Appendix B).

Considering that the sequence of AF078166 has only 70% and 71% identity to SEQ ID NO:13 and 15, respectively, it is clear that the alignments given by the Examiner do not support the assertion that SEQ ID NO:13 and 15 will hybridize to AF078166 under the stringent conditions recited in original claims, because the conditions of "0.2x SSC, 65°C" is generally considered as "high stringency" (see attached Google search result, Appendix C). Therefore, the Examiner's opinion is not reasonably supported by the evidence in the record.

In conclusion, Applicants have amended the claims to recite hybridization conditions which are shown to separately detect Lmx1a and Lmx1b (the gene described by Smidt). In addition, the evidence provided by the Examiner does not properly establish that sequence described by Smidt would hybridize under the conditions recited in the claims prior to this amendment. In view of the above, the rejection is clearly improper and should be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 9-10 and 12 stand rejected for allegedly being obvious over Smidt (2000) in view of Holzschuh (2001). Smidt is cited for teaching a method of using an Lmx1b polynucleotide, but fails to teach the addition step of detecting the DAT gene. Holzschuh allegedly provides the teaching missing from Smidt. As noted above, however, the claims have been amended to clarify that the polynucleotides being detected are distinct from the Lmx1b genes described in Smidt. Since these polynucleotides are neither disclosed nor suggested by the Smidt, the combination with Holzschuh cannot render the pending claims obvious. Withdrawal of the rejection is respectfully requested.

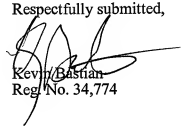
Claims 1, 9 and 11 also stand rejected for allegedly being obvious over Smidt (2000) because this reference also teaches detection of Nurr1 in dopaminergic neurons. As noted

above, however, Smidt fails to teach or suggest detection of the polynucleotides now claimed. Withdrawal of the rejection is respectfully requested..

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



Kevin Bastian
Reg. No. 34,774

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
KLB:dlh
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